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EDITORIAL

In time: human milk is the feeding strategy to prevent necrotizing enterocolitis

Em tempo: leite humano é a estratégia alimentar para prevenir a enterocolite necrosante

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Introduction

The challenge to meet the nutritional goals of the extremely low birth weight (ELBW) infant while attempting to avoid serious complications and adverse outcomes such as necrotizing enterocolitis (NEC) can be overcome with human milk.[1,2] Such a diet meets nutritional needs as well as provides health benefits to the recipient.

Mother's own milk

It has been demonstrated that a diet comprised of mother's own milk (MOM) is beneficial for ELBW infants because of its role in the protection from infection-related events, such as late onset sepsis (LOS), NEC, and urinary tract infection.[3-7] It has been found that the human milk-fed ELBW infant is protected even after their NICU stay. There are fewer readmissions to the hospital for respiratory illness through almost 3 years in those ELBW infants who received predominantly human milk during their NICU stay.[8]

There is a 50% reduction in the rate of NEC and/or LOS and a shortened length of hospital stay among the ELBW infants receiving MOM at an average daily dose of more than 50 mL/kg compared to MOM + formula, or formula alone.[3] That observation suggested that the dose of MOM (more than approximately 50mL/kg/day) was important to detect a beneficial health effect in ELBW infants.[3]

The concept of a "dose-dependent" protective effect of human milk has been reported elsewhere. ELBW infants receiving more than 50% MOM in the first 14 days after birth had an 83% reduction in the subsequent development of NEC compared to those receiving a diet of less than 50% MOM.[9] A daily intake of more than 50mL/kg for 4 weeks also is associated with a lower rate of neonatal sepsis.[10] The dose-dependent benefit should not be considered maximized at 50% intake. In a large retrospective analysis of 1272 infants, the likelihood of NEC or death after 14 days was decreased by a factor of 0.83 for each 10% increase in the proportion of total intake as human milk, suggesting the importance of dose and the predominance of a human milk diet.[11] Even earlier initiation of MOM, >50% of total intake, is associated subsequently with a lower incidence of NEC, sepsis, and/or death during the first 60 days after birth.[6] An even stronger prediction model was observed if the intake of MOM was more than 50% during days 6 to 10 after birth.[6] These studies

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suggest that in the ELBW population the important early protective effects of a human milk diet are long-lasting.

There are effects of human milk on the gastrointestinal tract of ELBW infants that account for the better acceptance of this milk when compared to formula. There are significantly fewer gastric residuals and less time feedings were withheld in infants receiving MOM versus formula.[3] Milestones, such as achievement of full enteral feeding and length of hospital stay, are significantly shortened with the feeding of MOM. These milestones are achieved in nearly twice as many days when the percentile of human milk intake was less than 20% as compared to more than 80%.[12]

Human milk feeding in ELBW infants also has been shown to protect against retinopathy of prematurity and, its most severe form, retinal detachment.[13,14] These observations support a role of human milk as an antioxidant as well as containing factors that affect angiogenesis.

Pathogenesis of NEC

Clinical studies demonstrate that human milk protects the ELBW infant from NEC. To understand this relationship it is important to describe a general overview of the pathogenesis of NEC. The etiology of NEC is unknown, but it is probably caused by multiple factors in a presumably genetically susceptible host. Factors implicated in its pathogenesis include prematurity (immature intestinal function), milk feeding (substrate), microbial colonization, impaired mucosal defense, and to some degree, circulatory instability. These factors act together to cause mucosal injury, which appears to be the initial event.[15,16]

Bacterial colonization plays a pivotal role in the pathogenesis of NEC. Colonization of the normal GI tract occurs rapidly after delivery. The normal colonization is altered by the NICU environment. Immature intestinal motility predisposes to bacterial overgrowth which is unchecked due to the coexistence of an immature mucosal host defense. Increased gastrointestinal permeability potentiates bacterial translocation. Intestinal signaling becomes disrupted. Thus, these factors support and promote the invasion of pathogenic organisms into the circulation and set up an immune activation with an intense intestinal inflammatory response.

Contributing to the pathogenesis of NEC, milk feeding serves as a substrate for bacterial proliferation in the gut. Organic acids, short chain fatty acids, carbon dioxide, and hydrogen gas are produced by bacterial fermentation milk component nutrients. These products of fermentation may be toxic to intestinal epithelium and increase intestinal distention. In animal studies using an intestinal loop model, addition of casein creates a favorable milieu for infiltration of cellular elements and vasoactive compounds, leading to mucosal injury.[17]

Human milk is protective

Preterm infants are susceptible to the development of NEC because immature immunologic and gastrointestinal systems result in altered host defense. Factors that contribute to innate resistance include luminal pH, enzymes, mucins, epithelial barriers, and gut motility, as well as nonspecific antimicrobial factors such as lactoferrin and lysozyme. Factors present in human milk play a protective role by reducing inflammation and the subsequent invasion of pathogenic bacterial species in the gastrointestinal tract. These factors include the enzyme platelet activating factor (PAF) acetylhydrolase, which blunts the immune activation sequence promoted by PAF. The local host defenses are enhanced by the addition of secretory IgA, lactoferrin, lysozyme, and cytokines (IL-10) from human milk. Components in human milk, such as epidermal growth factor, nucleotides, and glutamine also stimulate intestinal maturity.[18] Human milk antioxidants, such as vitamin E, carotene, and glutathione, also reduce oxidative stress.

Human milk oligosaccharides (HMO) are long chain sugars that constitute the third most prevalent component in human milk. HMOs are prebiotic agents that presumably act by enhancing proliferation of beneficial bifidobacterial species and preventing the adhesion of pathogenic bacteria to the intestinal epithelium. In animal models studied under conditions that produce NEC, the HMOs are found to prevent intestinal injury compared to synthetic oligosaccharides. Indeed, human milk diets and formula diets that were supplemented with HMOs prevent intestinal injury while diets of formula with or without synthetic oligosaccharides fail to prevent intestinal injury in the model.[19] The science of HMOs as luminal protective agents is intriguing.

Probiotics reduce NEC in neonates because they improve the intestinal barrier function, modulate the immune system, suppress the growth or epithelial binding and invasion, of pathogenic bacteria. It is likely that probiotics provide commensal bacterial colonization similar or additive to that promoted by human milk.

Conclusion

These data support recommendations of the American Academy of Pediatrics that encourage the use of MOM for all very low birth weight infants.[2] This recommendation is made to preclude the use of intact bovine protein formula in the preterm infant population. Given that newer human milk fortifiers not containing intact bovine protein are now available, the possibility of eliminating NEC with a diet of exclusive MOM can be realized.

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Conflicts of interest

The author declares no conflicts of interest.

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